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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/716,395	11/20/2000	Stephen W. Fesik	6752.US.01	8628

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EXAMINER

HARRIS, ALANA M

ART UNIT	PAPER NUMBER
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1642

17

DATE MAILED: 07/27/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

## Office Action Summary

**Application No.**

09/716,395

**Applicant(s)**

FESIK ET AL.

**Examiner**

Alana M. Harris, Ph.D.

**Art Unit**

1642

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

### Status

- 1) ☒ Responsive to communication(s) filed on April 30, 2004 as Paper number 15.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

### Disposition of Claims

- 4) ☒ Claim(s) 1-14 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☒ Claim(s) 14 is/are allowed.
- 6) ☐ Claim(s) 1-13 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

### Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

### Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- \* See the attached detailed Office action for a list of the certified copies not received.

### Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

## **DETAILED ACTION**

### ***Response to Arguments***

1. Claims 1-14 are pending.

Claims 1-14 are examined on the merits.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

### ***Drawings***

3. The Examiner acknowledges the submission of formal drawings on May 12, 2003 as Paper number 12. The draftsman will review these drawings.

### ***Maintained Rejections***

#### ***Claim Rejections - 35 USC § 112***

4. The rejection of claims 1, 2 and 4-13 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention is maintained.

"Applicants respectfully submit that they have provided sufficient written description of the invention as to reasonably convey to those of ordinary skill in the art at the time the invention was filed that they had possession of the claimed invention.", see Remarks/Arguments submitted April 30, 2004, page 4, second paragraph. Applicants reiterate their invention, as well as assert that the

Art Unit: 1642

specification not only teaches the size range and makeup of the replacement sequence, but also the size range of the mutant proteins. These arguments and points of view have been fully considered, but found unpersuasive.

"The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice...", see 1242 OG 174, column 1, section 2, January 30, 2001. Applicants have not set forth a representative number of species of a genus that embraces a plethora of proteins that can be regarded as mutant proteins derived from a wild-type human Bcl-2 protein. The claims set forth a genus, which includes mutant proteins with substantial variation. Applicants must describe a sufficient variety of species to reflect the variation within the genus. Applicants' specification only supports one mutant polypeptide consisting of 166 amino acids defined as SEQ ID NO: 2. SEQ ID NO:2 comprises a replacement amino acid sequence, SEQ ID NO: 1 consisting of 16 amino acids, therefore the written description is not commensurate in scope with the claims drawn to the said broadly claimed mutant protein. There is no disclosure, beyond the mere mention of possible other mutants is made in the specification. For the reasons of record and set forth above the rejection is maintained.

5. The rejection of claims 1, 2 and 4-13 under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention is maintained.

Art Unit: 1642

Applicants argue that the present specification complies with the legal requirement and set forth a brief summary of their invention for the Examiner. Applicants also pointedly express where in the specification information for preparation of the mutants and screening assays using the proteins of the invention can be found. These arguments and points of view have been carefully considered and have been found unpersuasive.

Applicants have not provided sufficient guidance enabling the effective implementation of the broadly claimed mutant proteins in screening assays to identify compounds useful as anti-cancer agents for treating disorders associated with cancer and other diseases caused by the impairment of the apoptotic process. Applicants have not provided sufficient evidence revealing a manageable pool of mutant proteins in which to implement in the assays discussed in the specification. The specification does not provide sufficient guidance on how to make these specific mutant proteins, which must comprise a flexible loop that is replaced with a replacement amino acid sequence comprising at least two acidic amino acids. These broadly claimed proteins would be cumbersome to make and use in a manner reasonable correlated to the applications set forth in the specification. This rejection is maintained because of the reasons set forth above and presented in the first action on the merits (FAOM) mailed March 26, 2003. Without guidance as to how to ascertain a manageable pool of uncharacterized mutant proteins, make these proteins and use these proteins the broadly claimed invention is unpredictable and the

Art Unit: 1642

experimentation left to those skilled in the art is unnecessarily and improperly extensive and undue.

6. The rejection of claims 1-13 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is maintained.

Applicants argue that the specification describes a flexible loop and point out Figures 1-3. Applicants assert that those of ordinary skill in the art would fully understand the metes and bounds of the invention. These arguments have been carefully considered but found unpersuasive. The Examiner has reviewed the specification, particularly pages 6 and 7 and the figure captions listed on 4, lines 7-16. In the figure captions there is no mention of a flexible loop, as well as page 6, lines 17-28. The specification seems to identify the flexible loop by ambiguous amino acids that are not clearly defined. Applicants also assert "...that the flexible loop of Bcl-x is not required either for maintaining the integrity of the protein or retaining function. Due to sequence homology, the same is presumed true for the Bcl-2 flexible loop." These assertions and arguments have been carefully considered, but found unpersuasive.

a. The recitation "flexible loop" in claims 1, 2 and 9 is vague and indefinite. It follows that the loop is essential to the wild-type and mutant human Bcl-2 proteins, however it is not clear what defines the loop, i.e. amino acid residues, structural juxtaposition. Applicants are requested to further clarify the flexible loop.

Art Unit: 1642

b. Claim 2 is vague and indefinite in the recitation "at least a portion of a flexible loop". It remains unclear how many amino acids coding for the flexible loop would be necessary to maintain structure and function. And while Applicants submit that the flexible loop of Bcl-x is not required for maintaining the integrity of the protein or retaining function this does not absolve the instant rejection. The term, flexible loop is still nebulous and lacks adequate description and characterization. Accordingly, the metes and bounds are unclear.

***Claim Rejections - 35 USC § 102***

7. The rejection of claims 1-8 and 10-13 under 35 U.S.C. 102(e) as being anticipated by U.S. Patent number 6,214,986 (filing date June 2, 1999) is maintained.

Applicants argue that the patent does not disclose a mutant protein as claimed by Applicants, but rather only the wild-type of Bcl-x<sub>L</sub>. Applicants' differentiate between their claimed protein and Sequence 2 in columns 51 and 53 of the patent. These points of view and arguments have been carefully considered, but found unpersuasive.

The claims are given the broadest interpretation. Applicants' claims read on a mutant protein derived from a wild-type Bcl-2 protein. In light of the terms, "mutant" and "derived" one of ordinary skill in the art clearly infers that there are changes and variations in the amino acid sequence. Applicants' independent claim is remiss of a sequence identifier and includes details of the protein based on limited structure in which this element is met by the prior art. Sequence 2 of

Art Unit: 1642

patent '986 is representative of a human mutant protein containing a replacement amino acid sequence comprising at least two acidic amino acids instead of the wild-type's amino acid residues corresponding to a flexible loop. The replacement amino acid sequence comprises at least 16 amino acid residues of Applicants' SEQ ID NO: 1 as established in the databases sheets included with the FAOM. The disclosed mutant protein reads on Applicants' broadly claimed mutant protein possessing all the properties of that claimed. The instant rejection is maintained for the reasons of record and set forth in the FAOM.

8. The rejection of claims 1-8 and 10-13 under 35 U.S.C. 102(b) as being anticipated by U.S. Patent number 5,646,008 (July 8, 1997) is maintained.

Applicants argue that "[c]ontrary to the Examiner's assertion, SEQ ID NO: 7 of the '008 patent is not a mutant Bcl-2 protein, but rather a mutant Bcl-x<sub>L</sub> protein...". In conclusion Applicants assert that SEQ ID NO: 7 is not a disclosure of the claimed invention. These points of view have been carefully considered, but found unpersuasive.

As noted in the maintained 102(e) rejection above a mutant protein derived from a wild-type human Bcl-2 protein is claimed. This variant sequence contains a flexible loop, which is replaced with a replacement amino acid sequence defined as SEQ ID NO: 1. Clearly the claimed protein is inapposite of a wild-type protein and the amino acid sequence changes are not defined in the broad claim. The anticipatory protein is a mutant as seen on the previously provided database sheet. It contains the replacement amino acid sequence, 16



Art Unit: 1642

specific amino acid residues, which corresponds to Applicants' SEQ ID NO: 1

This mutant protein is the same as that claimed and Applicants have not presented evidence that demonstrates that this mutant protein does not possess the inherent qualities of the claimed invention. Accordingly, the rejection is maintained.

9. The rejection of claims 1-8 and 10-13 under 35 U.S.C. 102(b) as being anticipated by Boise et al. (Cell 74: 597-608, August 27, 1993/ IDS reference C3) is maintained.

Applicants aver that the Examiner has misunderstood the teachings of Boise and nothing in the reference teaches, suggests or enables a mutant Bcl-2 protein. These points of view have been carefully considered, but found unpersuasive.

Applicants arguments directed to a deletion within the flexible loop of bcl-x<sub>L</sub> are not understood. Moreover, Applicants' attention is directed to Figure 3 on page 599 of Boise, specifically the mutant protein deemed, bcl-x<sub>L</sub>. This sequence was presented in the sequence alignment provided with the FAOM. This anticipatory sequence contains a flexible loop, which is replaced with a replacement amino acid sequence, SEQ ID NO: 1 as dictated by the claims. The replacement amino acid sequence, amino acid residues 29-44 corresponds with Applicants' SEQ ID NO: 1, see database sheets provided with the FAOM. SEQ ID NO: 1 is comprised within amino acid sequences that are different from the wild-type human Bcl-2 protein and the protein in its entirety is regarded as a

Art Unit: 1642

mutant protein. The disclosed mutant protein reads on Applicants' broadly claimed mutant protein possessing all the properties of that claimed. The instant rejection is maintained for the reasons of record and set forth in the FAOM.

10. The rejection of claims 1-8 and 10-13 under 35 U.S.C. 102(b) as being anticipated by Muchmore et al. (Nature 381:335-341, May 23, 1996/ IDS reference C7 is maintained.

Applicants aver "...the Muchmore reference is merely a sequence alignment of wild-type Bcl-2 family members" and Muchmore discusses deletion mutants including those having a deletion in the flexible loop. These points of view have been carefully considered, but found unpersuasive.

The disclosed mutant protein contains a replacement amino acid sequence comprising at least two acidic amino acids instead of the wild-type's amino acid residues corresponding to a flexible loop, see attached database sheet. The replacement amino acid sequence comprises at least 16 amino acid residues of Applicants' SEQ ID NO: 1, see attached database sheet. Giving the claims the broadest interpretation the prior art's mutant protein reads on Applicants' mutant protein. Applicants' claimed mutant protein does not limit what amino acids are replaced, substituted, deleted or mutated. Claim 1 does set forth that the flexible loop is replaced with a replacement amino acid sequence, however those sequences are not defined. Notwithstanding, the disclosed mutant and derived protein comprises the replacement sequence, SEQ ID NO: 1 as set forth in dependent claim 3. The disclosed mutant protein reads

Art Unit: 1642

on Applicants' broadly claimed mutant protein possessing all the properties of that claimed. The instant rejection is maintained for the reasons of record and set forth in the FAOM.

11. Claims 9 and 14 are free of the art.

***Allowable Subject Matter***

12. Claim 14 is allowed.

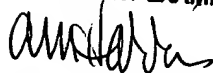
13. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Alana M. Harris, Ph.D. whose telephone number is (571) 272-0831. The examiner works a flexible schedule, however she can normally be reached between the hours of 6:30 am to 4:30 pm with alternate Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Art Unit: 1642

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

**ALANA M. HARRIS, PH.D.**  
**PRIMARY EXAMINER**



Alana M. Harris, Ph.D.  
20 July 2004